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All-Trans Retinoic Acid and Short-Time, High-Dose Cytarabine in Two Children With Acute Promyelocytic Leukemia

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We report on two girls, 3 and 13 years old, with acute promyelocytic leukemia (APL) who were successfully treated with all-trans retinoic acid (ATRA) 45 mg/m^2/day. "Retinoic acid syndrome" was prevented with short-time treatment of high dose (4 × 1.5 g/m^2) cytarabine. This regimen was well tolerated, although both children were critically ill. They achieved a complete remission confirmed by light microscopy, but reverse transcriptase polymerase chain reaction remained positive after ATRA, underlining the need of further chemotherapy. © 1996 Wiley-Liss, Inc.

Key words: acute promyelocytic leukemia, high dose cytarabine, retinoic acid syndrome, tretinoin therapy

INTRODUCTION

Acute promyelocytic leukemia (APL) FAB-M3 represents only 5% of all cases of acute nonlymphocytic leukemia in childhood [1]. Although APL is sensitive to chemotherapy, the course of initial treatment is frequently complicated by severe coagulopathy. More than 90% of the patients show features of disseminated intravascular coagulation (DIC) and 20–40% die early of fatal hemorrhage [2,3]. Bleeding diathesis is probably due to the release of procoagulatory and fibrinolytic substances from damaged leukemic cells [4]. An acquired alpha-2-antiplasmin deficiency was reported [5]. Without the life-threatening haemorrhagic diathesis, prognosis of APL is good. Remission induction with ATRA in patients with APL was reported for the first time in China, where complete remission was obtained in 100% of cases [6]. These excellent results were confirmed in several studies, mostly in adults [7,8].

An unresolved problem in treatment of APL consists in the development of "retinoic acid syndrome" (RAS) [9,10]. Little is known about prevention of this potentially fatal complication. Here we report our experiences in two severely ill children with APL who were successfully induced into remission with ATRA and in whom RAS could be prevented by application of short-time, high-dose cytarabine in both children [11].

CASE REPORTS

Case 1

A 3-year-old girl was presented because of a 3-month history of mild bleeding diathesis. She had recurrent febrile episodes and had lost 3 kg in weight. On admission she presented with extreme anemia and mucosal and cutaneous hemorrhages. Liver, spleen, and lymph nodes were not enlarged. A 2/6 cardiac murmur could be detected.

Laboratory investigations were: RBC 0,63 × 10^{12}/l, haemoglobin 2,1 g/dl, WBC 4.6 × 10^9/l; differential count: 94% lymphocytes, 1% myelocytes, 2% erythroblasts, 3% blast cells, platelets 10 × 10^9/l. Coagulation tests showed: PTZ 70%, PTT 24 sec, fibrinogen 219 mg/dl, antithrombin III 95%, fibrinogen split products 4,0 µg/dl, GOT 390 U/l, GPT 170 U/l, cholinesterase 2360 U/l, LDH 1260 U/l. All other routine laboratory tests were within normal range. Parvovirus IgG und IgM antibodies were positive 5 days after admission. Chest X-ray showed congested heart failure with signs of pulmonary edema.

Echocardiography indicated dilated hypokinetic left ventricle, with reduced shortening fraction 28%, small

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pericardial effusion, and dilated liver veins before transfusion. Bone marrow aspiration revealed 62% heavily granulated blasts with Auer rods, which showed strong positivity for peroxydase. Immunophenotypic findings indicated that the blasts were positive for CD33 in 90%, CD13 in 85%, CDw65 in 80%, respectively, and negative for CD11, CD14, CD15, CD34, and HLADr. They revealed a 46 XX t(15;17) karyotype. By RT-PCR performing on samples from bone marrow and peripheral blood PML/RAR gene fusion transcripts could be detected. Erythrocytes and platelets were transfused. Further treatment consisted of digoxin, furosemid, and amoxicillin. Her clinical condition and respiratory function deteriorated and she required mechanical ventilation. The initial oliguric acute renal failure was successfully treated with dopamin and diuretics. In the following 6 days, the girl received five platelet and two red cell transfusions and one fresh frozen plasma. Despite platelet substitution, she had mucosal bleedings and gross hematuria during the first 2 days.

After consolidation of her clinical condition, ATRA therapy was started on day 7. ATRA was administered in two daily doses at 45 mg/m^2. On day 5 of treatment, the white cell count reached 10.4 $\times$ 10^9/l. Bilateral papilledema developed and was diagnosed as a symptom of increased intracranial pressure and related to an early RAS. To prevent a further increase of leucocytes and possible progressive RAS, cytotoxic chemotherapy was added. On days 6 and 7 of ATRA therapy, the patient received 4 $\times$ 1.5 g/m^2 cytarabine every 12 hours. Fibrinogen split products decreased immediately to values between 2 and 1 μg/ml. The bleeding diathesis stopped within 3 days. Bone marrow aspiration on day 35 revealed a hypocellular bone marrow in complete remission, defined as absence of blast cells and a normal peripheral blood count. Molecular analysis of bone marrow still demonstrated the PML/RAR gene fusion transcript by means of RT-PCR. After 69 days of ATRA, chemotherapy according to the AML-BFM 93 protocol was started. PCR negativity for PML/RAR could be achieved and the patient is still in remission 2 months after the end of chemotherapy.

Case 2

A 13-year-old girl was presented because of a 2-month history of recurrent febrile episodes and cutaneous bleedings. Liver, spleen, and lymph nodes were not enlarged.

Laboratory investigations indicated: RBC 2.85 $\times$ 10^{12}/l, haemoglobin 8.9 g/dl, WBC 0.9 $\times$ 10^9/l with 80% lymphocytes, 17% granulocytes, 2% blast cells, platelets 16 $\times$ 10^9/l, PTZ 70%, PTT 37 sec, fibrinogen 52 mg/dl, antithrombin III 95%, fibrinogen split products 1.0 μg/dl. Bone marrow examination revealed 90% blasts with multiple Auer rods, which showed 100% positivity for peroxydase. CD33 was found in 85%, CD13 in 85%, CD15 in 10%, and CDw65 in 25% of blasts and were negative for CD11, CD14, CD34, and HLADr. Routine cytogenetics revealed a 46 XX t(15;17) karyotype. A PML/RAR gene fusion transcript was detected by RT-PCR studies. ATRA was administered in two daily doses at 45 mg/m^2. Fibrinogen split products were negative on day 5 of ATRA therapy, and no bleeding episode was observed. On day 10 of treatment, the girl complained of a severe headache. Within 1 day, the WBC increased from 1.3 to 7.6 $\times$ 10^9/l. Although no other signs of RAS developed, 2 $\times$ 10 mg dexamethasone were given. To prevent a further WBC increase, treatment with 4 $\times$ 0.75 g/m^2 cytarabine in a 12-hour interval was started. Within 1 day the headache disappeared. After cytarabine the WBC stayed low for 2 weeks, when an increase to 21 $\times$ 10^9/l was observed. Cytarabine was repeated in the same dosage. Bone marrow examination on day 38 of induction treatment revealed a hypocellular bone marrow in complete remission. PML/RAR gene fusion product could still be detected by RT-PCR. The patient is now on cytotoxic chemotherapy according to the BFM-AML 93 protocol.

DISCUSSION

In 1976, a deletion of the long arm on chromosome 17 was demonstrated in two APL patients [12]. In 1977, this deletion was identified as balanced t(15;17) translocation [13]. The breakpoint on chromosome 17 was localized within the retinoic acid receptor gene (RAR), whereas the breakpoint on chromosome 15 has been localized within the PML gene [14,15]. Alternatively, this RAR/PML fusion product contributed to promyelocytic leukemogenesis [16]. Both patients with APL had the characteristic (15;17) translocation with a breakpoint on chromosome 17 in the region of the RAR alpha. Although APL is very sensitive to chemotherapy, up to 40% die of hemorrhagic complications [2,3]. The first patient was critically ill. Extreme low erythrocyte counts with multiorgane failure was due to a concurrent parvovirus infection. She also had a bleeding diathesis.

Of 26 patients reviewed after chemotherapy for t(15;17) positive APL, nine were children. Five children died of hemorrhagic complications and one because of an infection during induction treatment. Three patients are alive, two after autologous-, one after allogeneic bone marrow transplantation [2].

The good prognosis of APL is jeopardized by complications. High efficacy of ATRA to induce remission in patients with APL has been shown [6–8]. ATRA acts by triggering differentiation rather than by a cytotoxic effect on the leukemic clone [17]. The clinical response is asso-

ciated with maturation of the leukemic clone to granulocytes and makrophages [6,7].

In these studies, ATRA also corrected the coagulation abnormalities. In a phase I study, the maximum tolerated ATRA dose was 60 mg/m^2/day given twice daily [18]. With a lower ATRA dose (25 mg/m^2/day), there was no difference in terms of therapeutic efficacy, but the frequency of hyperleucocytosis and RAS was not reduced [19]. We started ATRA therapy with the recommended dose of 45 mg/m^2 in both patients, and bleeding diathesis stopped within 3 days. The increase of leucocytes in both girls in combination with an increase of intracranial pressure in Case 1 prompted us to add short-time intensive chemotherapy with high-dose cytarabine to prevent RAS [11].

Nine of 35 adult patients treated with ATRA developed a syndrome consisting of respiratory distress, fever, edema, pleural and pericardial effusions, and hypotension 2–21 days after initiation of therapy [9]. Autopsy has revealed extensive infiltration of myeloid cells into the organs. Although leucocytosis was frequently observed with this symptom complex, the reaction may occur with a normal leukocyte count in up to one-third of the cases [9,10]. In three of nine children treated with ATRA, RAS was associated with the highest leukocyte counts (53-, 82-, and 98 G/l) [20]. Neither cessation of therapy nor leucapheresis was useful in the management of this complication. Only early dexamethason substitution resulted in some improvement [9]. Close follow-up is necessary during the first 3 weeks, especially in patients with hyperleucocytosis. In Case 2, a lower initial cytarabine dose was chosen to prevent WBC increase. Because of a further WBC increase 2 weeks later, the cytarabine regimen had to be repeated.

Retrospectively, no further signs of RAS were observed after 4 × 1.5 g/m^2 cytarabine in both patients. Thus we recommend cytarabine during induction treatment, when a WBC increase is observed, to prevent hyperleukocytosis and a possible RAS in pediatric patients. We believe that our chosen regimen can be used in critically ill patients as shown in Case 1. Even under the worst clinical conditions, induction therapy with ATRA was well tolerated.

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